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*R. Mahoney*  
7 April 2003

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The Patent Office

Cardiff Road  
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1. Your reference

143976

2. Patent application number

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0206255.2

3. Full name, address and postcode of the or of each applicant (underline all surnames)

BTG International Limited

10 Fleet Place  
Limeburner Lane  
London  
EC4M 7SB

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

GB

GB

808 400 6001

4. Title of the invention

NOVEL SALT FORMS

5. Name of your agent (if you have one)

ENGLAND, Christopher David

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

BTG International Limited  
IP Business Services  
10 Fleet Place  
Limeburner Lane  
London  
EC4M 7SB  
GB

Patents ADP number (if you know it)

7745771001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number  
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Date of filing  
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or yes

b) there is an inventor who is not named as an applicant, or

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Description

9 ✓

Claim(s)

2 ✓

Abstract

1 ✓

Drawing(s)

3 + 3 ✓ *gmm*

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

1 ✓

Request for substantive examination (Patents Form 10/77)

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

*CD gmm*

Date

C D ENGLAND

15 March 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Barry Turner 020 7575 1583

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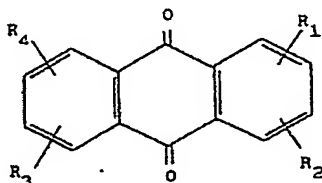
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## NOVEL SALT FORMS

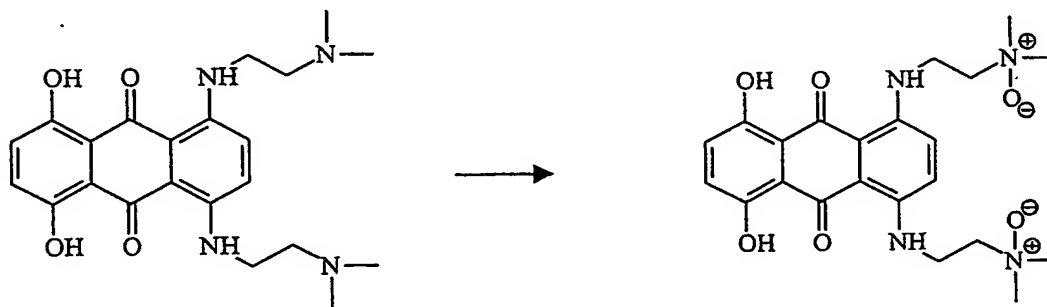
The invention relates to novel salt forms of anthraquinone derivatives such as AQ4N, a bis-bioreductive agent with value in the treatment of cancer.

WO-A-91/05824 (National Research Development Corporation discloses a  
5 compound of formula (I):



in which R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are each separately selected from hydrogen, X, NH-A-NHR and NH-A-N(O)R'R'' wherein X is hydroxy, halogeno, amino, C<sub>1-4</sub> alkoxy or C<sub>2-8</sub> alkanoyloxy, A is a C alkylene group with a chain length between NH  
10 and NHR or N(O)R'R'' of at least 2 carbon atoms and R, R' and R'' are each separately selected from C<sub>1-4</sub> alkyl groups and C<sub>2-4</sub> hydroxyalkyl and C<sub>2-4</sub> dihydroxyalkyl groups in which the carbon atom attached to the nitrogen atom does not carry a hydroxy group and no carbon atom is substituted by two hydroxy groups, or R' and R'' together are a C<sub>2-6</sub> alkylene group which with the nitrogen atom to which R' and  
15 R'' are attached forms a heterocyclic group having 3 to 7 atoms in the ring, the compound optionally being in the form of a physiologically acceptable salt.

A preferred compound within this general formula is the *N*-oxide AQ4N, which would normally be synthesised by oxidation of AQ4:



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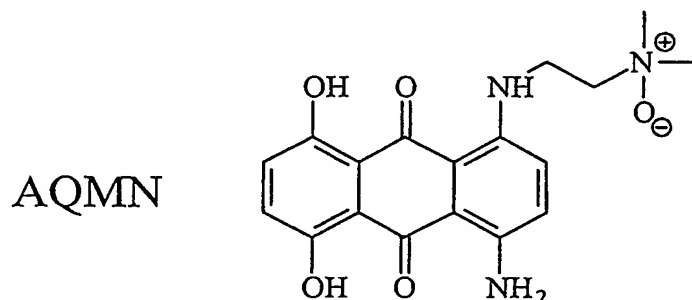
AQ4

AQ4N

AQ4N is in fact a prodrug and the reverse reaction occurs in vivo, reductive metabolism in hypoxic cancer cells giving the active agent, AQ4, in its protonated form. The prodrug is relatively non-toxic when compared with the active agent, AQ4, making it particularly attractive for administration as a pharmaceutical. However, it

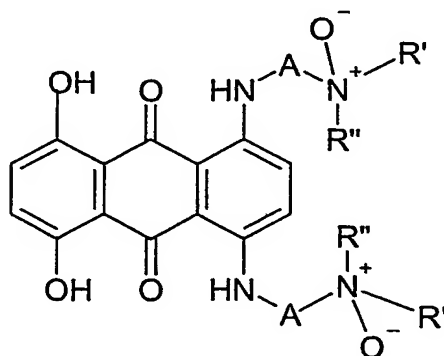
does not readily give a crystalline form, and it is therefore desirable to prepare and formulate it for administration in the form of a salt.

AQ4N has up to now been reported in the form of a dihydrochloride salt AQ4N.2HCl. See for example *J. Chem. Soc., Perkin Trans. I*, 1999, 2755-2758 (Lee *et al.*) and WO-A-00/05194. However, investigations of AQ4N.2HCl raw material have demonstrated significant quantities of an impurity, denoted AQMN, which has been characterised by LCMS:



This impurity can be formed by degradation of AQ4N, and more significantly show an undesirable level of cytotoxicity, generally being higher than that of AQ4N itself. This level of cytotoxicity is to be avoided in a compound which is intended to be administered in the form of a relatively non-toxic prodrug.

We have now found that the above problem may be avoided by preparing, formulating and administering the compound in a salt form other than with a strong acid such as hydrochloric acid. Thus according to the present invention there is provided a compound of formula (I):



in which A is a C alkylene group with a chain length between NH and N(O)R'R'' of at least 2 carbon atoms and R' and R'' are each separately selected from C<sub>1-4</sub> alkyl groups and C<sub>2-4</sub> hydroxyalkyl and C<sub>2-4</sub> dihydroxyalkyl groups in which the carbon atom attached to the nitrogen atom does not carry a hydroxy group and no carbon

atom is substituted by two hydroxy groups, or R' and R'' together are a C<sub>2-6</sub> alkylene group which with the nitrogen atom to which R' and R'' are attached forms a heterocyclic group having 3 to 7 atoms in the ring,

- characterised in that the compound is in the form of a salt with a physiologically acceptable acid having a pK<sub>a</sub> in the range of 2.0 to 9.0.

The compounds (I) will be used in the form of a physiologically acceptable salt which will be an acid addition salt with an organic or inorganic acid. Physiologically acceptable acids having a pK<sub>a</sub> in the range of 2.0 to 9.0 may be drawn from the following Table 1:

10

**Table 1: pK<sub>a</sub> values of some common acids**

Free Acid or Base	pK <sub>a</sub> at 25 °C
Maleic	2.00 (pK <sub>a1</sub> )
Benzenhexacarboxylic (mellitic)	2.08 (pK <sub>a1</sub> )
Phosphoric	2.12 (pK <sub>a1</sub> )
Brucine tetrahydrate	2.30 (pK <sub>a1</sub> )
Benzenepentacarboxylic	2.34 (pK <sub>a1</sub> )
Glycine	2.34 (pK <sub>a1</sub> )
Benzene-1,2,4,5-tetracarboxylic (pyromellitic)	2.43 (pK <sub>a1</sub> )
Malonic	2.85 (pK <sub>a1</sub> )
Phthalic	2.90
Salicylic	2.98
Benzene-1,2,3-tricarboxylic (hemimellitic)	2.98 (pK <sub>a1</sub> )
Tartaric	3.02 (pK <sub>a1</sub> )
Fumaric	3.03 (pK <sub>a1</sub> )
Glycylglycine	3.06
Citric acid	3.06 (pK <sub>a1</sub> )
Cyclopentanetetra-1,2,3,4-carboxylic	3.07 (pK <sub>a1</sub> )
o-Phthalic	3.10 (pK <sub>a1</sub> )
Benzene-1,2,4,5-tetracarboxylic (pyromellitic)	3.13 (pK <sub>a1</sub> )
Benzene-1,3,5-tricarboxylic (trimesic)	3.16 (pK <sub>a1</sub> )
Dimethylmalonic	3.29 (pK <sub>a1</sub> )
Mandelic	3.36
Butane-1,2,3,4-tetracarboxylic	3.36 (pK <sub>a1</sub> )
Malic	3.40 (pK <sub>a1</sub> )
1,1-Cyclohexanediactic	3.52 (pK <sub>a1</sub> )
2-Methylpropane-1,2,3-tricarboxylic	3.53 (pK <sub>a1</sub> )
Hippuric	3.64
Propane-1,2,3-tricarboxylic (tricarballic)	3.67 (pK <sub>a1</sub> )
Formic	3.75
3,3-Dimethylglutaric	3.79 (pK <sub>a1</sub> )
1,1-Cyclopentanediacetic	3.82 (pK <sub>a1</sub> )
Itaconic	3.84 (pK <sub>a1</sub> )
Lactic	3.86

Free Acid or Base	pK <sub>a</sub> at 25 °C
Barbituric	3.98
Ascorbic	4.10 (pK <sub>a1</sub> )
2,2-Dimethylsuccinic	4.11 (pK <sub>a1</sub> )
Succinic	4.19 (pK <sub>a1</sub> )
Benzoic	4.20
3,6-Endomethylene-1,2,3,6-tetrahydrophthalic acid "EMTA"	4.30 (pK <sub>a1</sub> )
2,2-Dimethylglutaric	4.31 (pK <sub>a1</sub> )
Acetic	4.76
<i>n</i> -Butyric	4.82
Propionic	4.87
Pyridine	5.23
Hydroxylamine	6.03
Bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane "BIS-TRIS"	6.46
Imidazole	7.00
2-(Aminoethyl)trimethylammonium chloride "CHOLAMINE"	7.10
2-Hydroxyethyliminotris(hydroxymethyl)methane "MONO-TRIS"	7.83
4-(2-Hydroxyethyl)-1-piperazinepropane sulfonic acid "EPPS"	8.00

as well as other available acids such as methanesulfonic acid, *p*-toluenesulfonic acid and gluconic acid, all of which have a pK<sub>a</sub> of less than 6.

Preferably the physiologically acceptable acid has a pK<sub>a</sub> in the range of 2.0 to 6.0. Preferably the physiologically acceptable acid is selected from the group consisting of methanesulfonic acid, *p*-toluenesulfonic acid, phosphoric acid, citric acid, tartaric acid, succinic acid and gluconic acid.

More preferably the physiologically acceptable acid has a pK<sub>a</sub> in the range of 3.0 to 6.0. The physiologically acceptable acid may especially be an organic acid, particularly an organic mono- or di-acid, and especially one selected from the group consisting of methanesulfonic acid, succinic acid, citric acid, gluconic acid and tartaric acid.

A in formula (I) may be branched but is conveniently a straight chain alkylene group, i.e. tetramethylene, especially trimethylene, or particularly ethylene.

R' and R" may also have a branched carbon chain but are conveniently straight chain whether they are alkyl groups or hydroxy-substituted alkyl groups. When R' or R" is a monohydroxyalkyl group this is conveniently substituted terminally and when R' or R" is a dihydroxyalkyl group this is conveniently substituted terminally by one of the hydroxy groups. When R' and R" are alkyl the preference is for a group of three or especially two or one carbon atoms and when R' and R" are hydroxy-substituted alkyl the preference is for the alkyl group to be of three carbon atoms or, in the case

of a monohydroxyalkyl group, alternatively of two carbon atoms. Examples of preferred individual groups R' and R" are CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH, CH(CH<sub>3</sub>)CH<sub>2</sub>OH and CH<sub>2</sub>CHOHCH<sub>2</sub>OH.

R' and R" will more usually be identical.

5 Alternatively, as indicated, R' and R" together with the nitrogen atom to which they are attached may represent a heterocyclic group —N(CH<sub>2</sub>)<sub>n</sub> where n is 2 to 6, i.e. aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl and perhydroazepin-1-yl, the smaller groups such as azetidin-1-yl and especially aziridin-1-yl being of most interest.

10 Specific groups NH—A—N(O)R'R" of particular interest are  
 NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH<sub>3</sub>)C<sub>2</sub>H<sub>5</sub>, NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>,  
 NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>,  
 NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH(CH<sub>3</sub>)CH<sub>2</sub>OH)<sub>2</sub>, NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH<sub>2</sub>CHOHCH<sub>2</sub>OH)<sub>2</sub> and  
 especially NH—(CH<sub>2</sub>)<sub>2</sub>—N(O)(CH<sub>3</sub>)<sub>2</sub>.

15 The salt with a physiologically acceptable acid may be prepared by any conventional means, for example by reaction of the organic base (I) with the appropriate inorganic or organic acid, usually by simple admixture in solution. The acid addition salts are generally crystalline solids which are relatively soluble in water, methanol, ethanol and similar solvents. One salt form may also be converted  
 20 into another by chromatography using a column which has been pre-treated with the desired physiologically acceptable acid.

The compounds (I) may be formulated with a physiologically acceptable diluent or carrier for use as pharmaceuticals for both veterinary and particularly human use by a variety of methods. For instance, they may be applied as a  
 25 composition incorporating a liquid diluent or carrier, for example an aqueous or oily solution, suspension or emulsion, which may often be employed in injectable form for parenteral administration and therefore may conveniently be sterile and pyrogen free. Oral administration may also be used and although compositions for this purpose may incorporate a liquid diluent or carrier, it is more usual to use a solid, for example a  
 30 conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate. Such solid compositions may take the form of powders but are more conveniently of a formed type, for example as tablets, cachets, or capsules. Alternative, more specialized types of formulation include liposomes and nanoparticles.



Other types of administration than by injection or through the oral route which are of use in both human and veterinary contexts include the use of suppositories or pessaries. Another form of pharmaceutical composition is one for buccal or nasal administration or alternatively drops for administration into the eye which may conveniently contain a sterile liquid diluent or carrier. Other formulations for topical administration include lotions, ointments, creams, gels and sprays.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions containing a unit dose, or a multiple or sub-unit of a unit dose.

Whilst the dosage of the compound used will vary according to the activity of the particular compound and the condition being treated, it may be stated by way of guidance that a dosage selected in the range from 25–500 mg/m<sup>2</sup> per day, particularly in the range from 50–300 mg/m<sup>2</sup> per day, will often be suitable although higher doses than this, for example in the range from 25–750 mg /m<sup>2</sup> per day, may be considered in view of the lower level of toxic side effects obtained with the compounds (I). This dosage regime may be continued for however many days is appropriate to the patient in question, the daily dosages being divided into several separate administrations if desired. Thus, for example, in the case of conditions such as advanced breast cancer, non-Hodgkin's lymphoma and hepatoma, treatment for one day followed by a repeated dose after an interval, such as 21 days, may be appropriate whilst for the treatment of acute non-lymphocytic leukaemia, treatment over 5 consecutive days may be more suitable. Alternatively, single administrations spaced by several days, for example one dose every two or three weeks, may be used.

The compounds (I) are of particular value for the treatment of cancer in warm blooded animals including humans. The compounds are of interest in relation to the treatment of solid tumours, such as various forms of sarcoma and carcinoma, and also for disseminated tumours such as leukaemias. Areas of particular interest are the treatment of breast cancer, lung cancer, prostate cancer, pancreatic cancer, and oesophageal cancer, and the treatment of non-Hodgkin's lymphoma and acute non-lymphocytic leukaemia. In the treatment of cancer, parenteral and sometimes topical administration is often of particular interest. Moreover, it may be advantageous to use the compounds (I) in a combined treatment, given separately or together in the same composition, with other anti-cancer agents, such as mitotic inhibitors, for example vinblastine; alkylating agents, for example cisplatin, carboplatin and cyclophosphamide; other antimetabolites, for example 5-fluorouracil, cytosine arabinoside

and hydroxyurea; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide and biological response modifiers, for example interferon. The compounds (I) may also be used in combined treatment with radiation therapy of the tumour.

- 5       The present invention thus includes a method for aiding regression and palliation of cancer which comprises administering to a patient a therapeutically effective amount of a compound (I) as defined hereinbefore.

In addition to their anti-cancer use the compounds (I) are of interest for various other pharmaceutical applications in view of their activity as chelating agents.

- 10       The invention is illustrated by the following Examples in which—

Figure 1 shows the first derivative of pH *versus* pH in a solution of AQ4N dihydrochloride;

Figure 2 shows the first derivative of pH *versus* NaOH molar equivalence under the same conditions; and

- 15       Figure 3 shows the increase in AQMN over incubation time in 5 mg/ml solutions incubated at 40°C.

## EXAMPLES

### **Example 1: Demonstration of the instability of AQ4N dihydrochloride— physico-chemical properties of AQ4N**

- 20       Changes in the pH of a solution of AQ4N dihydrochloride were monitored to demonstrate the degradation of AQ4N into AQMN. The pH curves are shown in Figures 1 and 2. Figure 1 shows a clear dissociation at between pH 7.7 and pH 9.4, and this equates to the dissociation events shown in Figure 2 at approximately 2 molar equivalence. A low pH dissociation event can be observed, speculatively  
25       assigned to a pH between 4.1 and 4.6 where the molar equivalence is between 0.95 and 1.15.

The physical nature of the low pH dissociation events can be assigned to dissociation of the benzylic amines in AQ4N to give the primary amine AQMN.

**Example 2: Demonstration of the instability of AQ4N dihydrochloride—  
AQ4N solution stability**

The degradation of AQ4N was investigated using 5 mg/ml solutions of AQ4N at a pH of 2.4, 4.5 and 6.8, which equated to water, 20 mM sodium acetate buffer and 20 mM sodium orthophosphate buffer, respectively. The primary degradation pathway of AQ4N is its conversion to AQMN. The increase in AQMN concentration in 5 mg/ml solutions incubated at 40°C is shown in Figure 3.

The degradation rates equate to a 0.84% (w.r.t. AQ4N), 0.19% (w.r.t. AQ4N) and 0.02% (w.r.t. AQ4N) increase in AQMN content per day under these conditions.

**Example 3: Demonstration of the cytotoxicity of AQMN**

The toxicity of a pure sample (99.3%) in the P388 system of AQ4N and AQMN were determined and the results obtained are presented in Table 2.

**Table 2: AQ4N and AQMN cytotoxicity values**

Compound	IC <sub>50</sub> P388 (nM)	Relative toxicity (normalised to AQ4N)
AQ4N	410	1.0
AQMN	77	5.2

Based on these data, AQMN has a cytotoxicity which is at least 5 times greater than that of AQ4N in the same system. The “greater than” modifier is required since all samples of AQ4N contain substantial percentages of AQMN, which will affect the toxicity result.

**Example 4: Preparation of 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-*N*-oxide L-tartrate (AQ4N tartrate)**

**(a) 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-*N*-oxide dihydrochloride (AQ4N.2HCl)**

A stirred solution of 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione (AQ4) (17.75 g, 43.1 mmol), prepared according to *J. Chem. Soc., Perkin Trans. I*, 1999, 2755-2758 (Lee *et al.*), in CH<sub>2</sub>Cl<sub>2</sub> / MeOH (5:1) (600 mL) was treated dropwise over 30 min with a solution of 2-benzene-

sulfonyl-3-phenyloxaziridine (Davis reagent: *J. Org. Chem.* 1982, 47, 1775) (25.7 g, 98.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL). After addition, the mixture was stirred at 20 °C in the dark for a further 90 min. It was then concentrated under reduced pressure at 24–26 °C (bath temperature) to ca. 100–200 mL, and then diluted successively with EtOAc (400 mL) and petroleum ether (400 mL). The homogeneous mixture was stirred at 20 °C for 15 min, then kept at -10 °C for 2 h. The blue precipitate was collected by filtration, washed with EtOAc / petroleum ether (1:1; 4 x 100 mL), and suctioned dry. It was then dissolved in MeOH (200 mL) and the solution was treated with anhydrous HCl gas until it remained acidic (pH ca. 2). After storing at -10 °C overnight, the precipitate was collected by filtration and washed successively with MeOH / EtOAc (1:1; 5 x 30 mL) and EtOAc (2 x 30 mL), and dried under vacuum to give AQ4N dihydrochloride (17.7 g, 80%), m.p. 243–245 °C. HPLC shows a purity of ca. 98.5%.

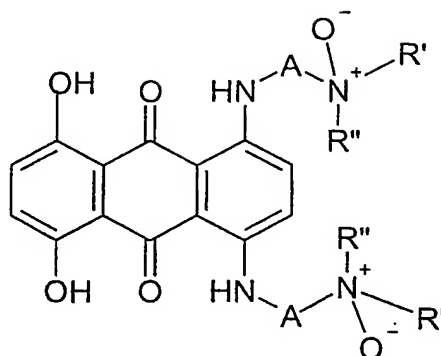
**(b) 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-*N*-oxide L-tartrate (AQ4N tartrate)**

A stirred solution of AQ4N dihydrochloride in water was basified with sodium hydroxide. The solution was extracted with EtOAc (400 mL) and petroleum ether (400 mL). The organic layers were suctioned dry and then dissolved in water (200 mL) and the solution was treated with L-tartaric acid crystals until it remained acidic (pH ca. 2). The water was allowed to evaporate off. After storing at -10 °C overnight, the precipitate was collected by filtration and washed successively with MeOH / EtOAc (1:1; 5 x 30 mL) and EtOAc (2 x 30 mL), and dried under vacuum to give AQ4N tartrate crystals.

The corresponding methanesulfonate, succinate, citrate, gluconate and tartaric salts may be made by an analogous procedure.

## CLAIMS

1. A compound of formula (I):



- in which A is a C alkylene group with a chain length between NH and N(O)R'R'' of at  
 5 least 2 carbon atoms and R' and R'' are each separately selected from C<sub>1-4</sub> alkyl  
 groups and C<sub>2-4</sub> hydroxyalkyl and C<sub>2-4</sub> dihydroxyalkyl groups in which the carbon  
 atom attached to the nitrogen atom does not carry a hydroxy group and no carbon  
 atom is substituted by two hydroxy groups, or R' and R'' together are a C<sub>2-6</sub> alkylene  
 group which with the nitrogen atom to which R' and R'' are attached forms a  
 10 heterocyclic group having 3 to 7 atoms in the ring,  
 characterised in that the compound is in the form of a salt with a  
 physiologically acceptable acid having a pK<sub>a</sub> in the range of 2.0 to 9.0.

2. A compound as claimed in claim 1 characterised in that the physiologically  
 15 acceptable acid has a pK<sub>a</sub> in the range of 2.0 to 6.0.

3. A compound as claimed in claim 2 characterised in that the physiologically  
 acceptable acid has a pK<sub>a</sub> in the range of 3.0 to 6.0.

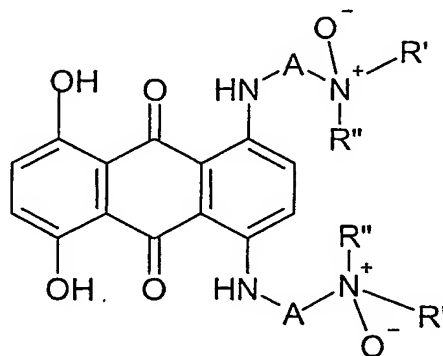
- 20 4. A compound as claimed in claim 3 characterised in that the physiologically  
 acceptable is an organic mono- or di-acid.

5. A compound as claimed in claim 4 characterised in that the physiologically  
 acceptable selected from the group consisting of methanesulfonic acid, succinic acid,  
 25 citric acid, gluconic acid and tartaric acid.

6. A compound as claimed in any preceding claim characterised in that A is a straight chain alkylene group.
7. A compound as claimed in any preceding claim characterised in that R' and  
5 R" are straight chain alkyl groups or hydroxy-substituted alkyl groups.
8. A compound as claimed in claim 7 characterised in that R' and R" are each CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub>.
- 10 9. A compound as claimed in claim 8 characterised in that each group of formula NH-A-N(O)R'R" is group of formula NH-(CH<sub>2</sub>)<sub>2</sub>-N(O)(CH<sub>3</sub>)<sub>2</sub>.
10. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 9 together with a physiologically acceptable diluent or  
15 carrier.
11. A compound of formula (I) as defined in any of claims 1 to 9 for use in therapy.

**ABSTRACT**  
**NOVEL SALT FORMS**

A compound of formula (I):



- 5 in which A is a C alkylene group with a chain length between NH and N(O)R'R'' of at least 2 carbon atoms and R' and R'' are each separately selected from C<sub>1-4</sub> alkyl groups and C<sub>2-4</sub> hydroxyalkyl and C<sub>2-4</sub> dihydroxyalkyl groups, or R' and R'' together are a C<sub>2-6</sub> alkylene group,

characterised in that the compound is in the form of a salt with a  
10 physiologically acceptable acid having a pK<sub>a</sub> in the range of 2.0 to 9.0.

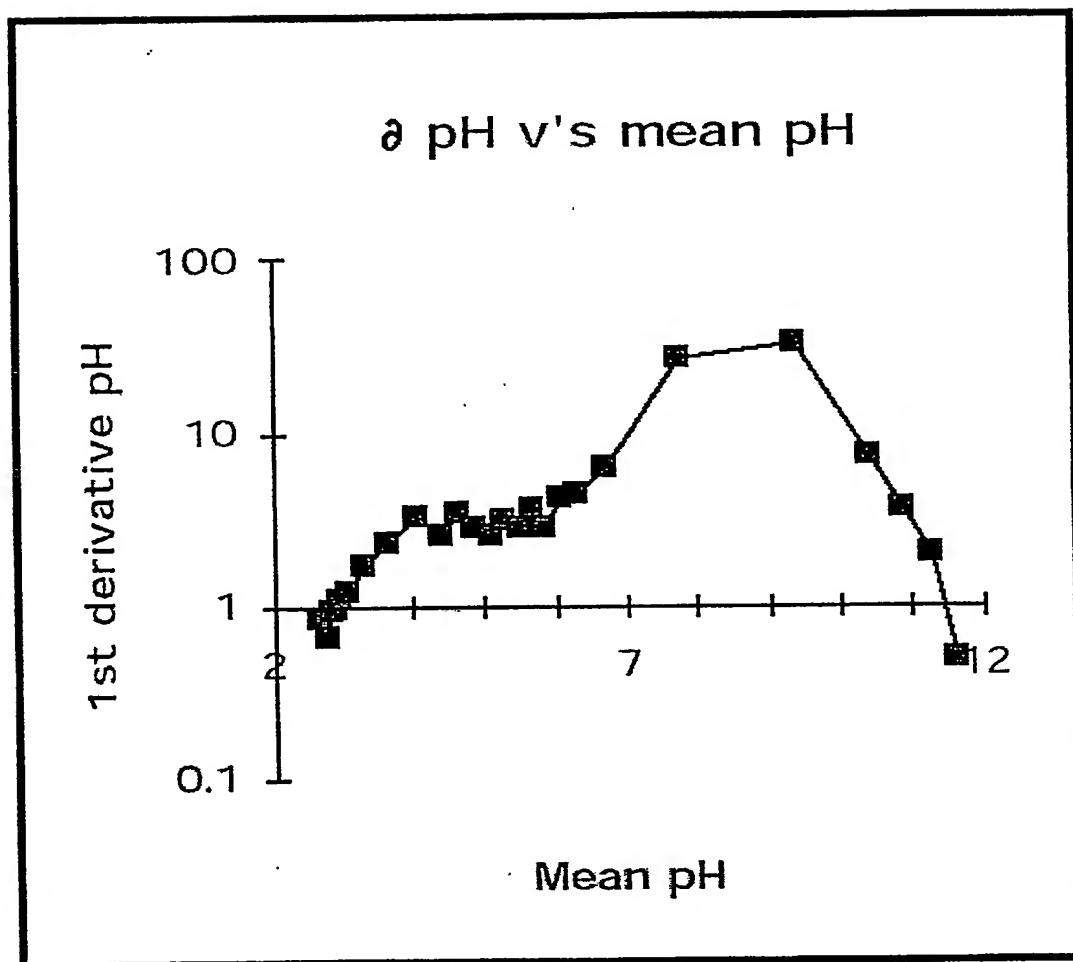


Figure 1



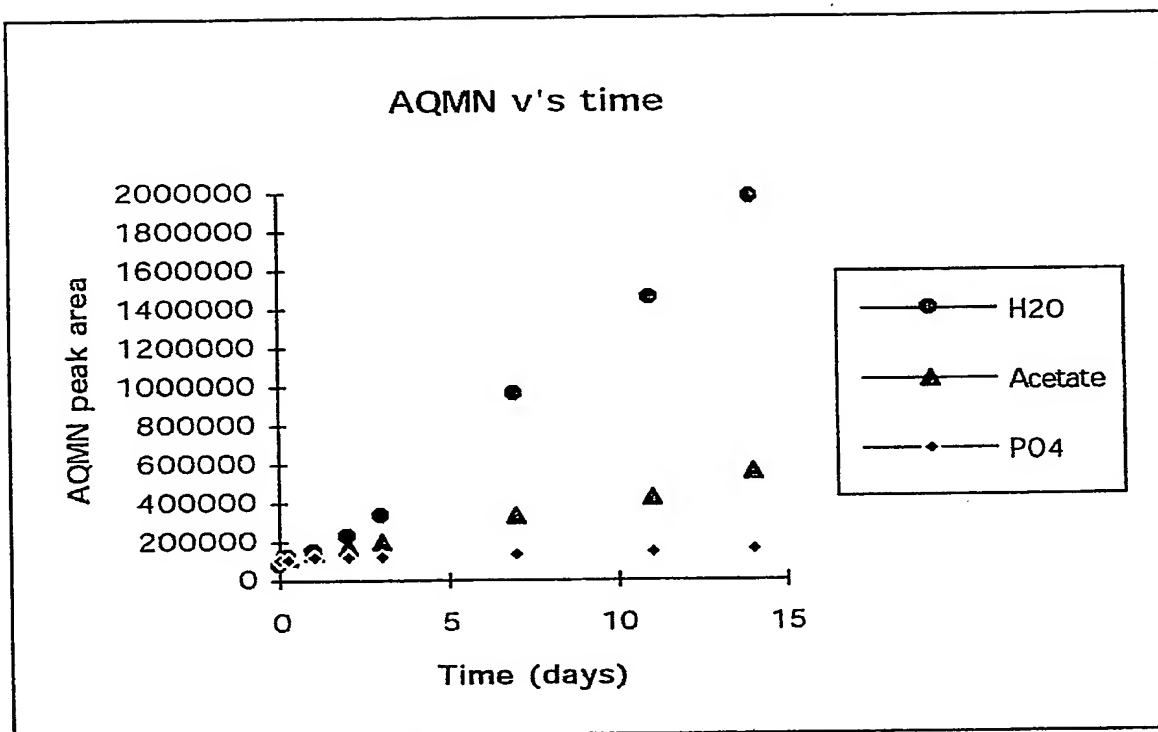


Figure 2

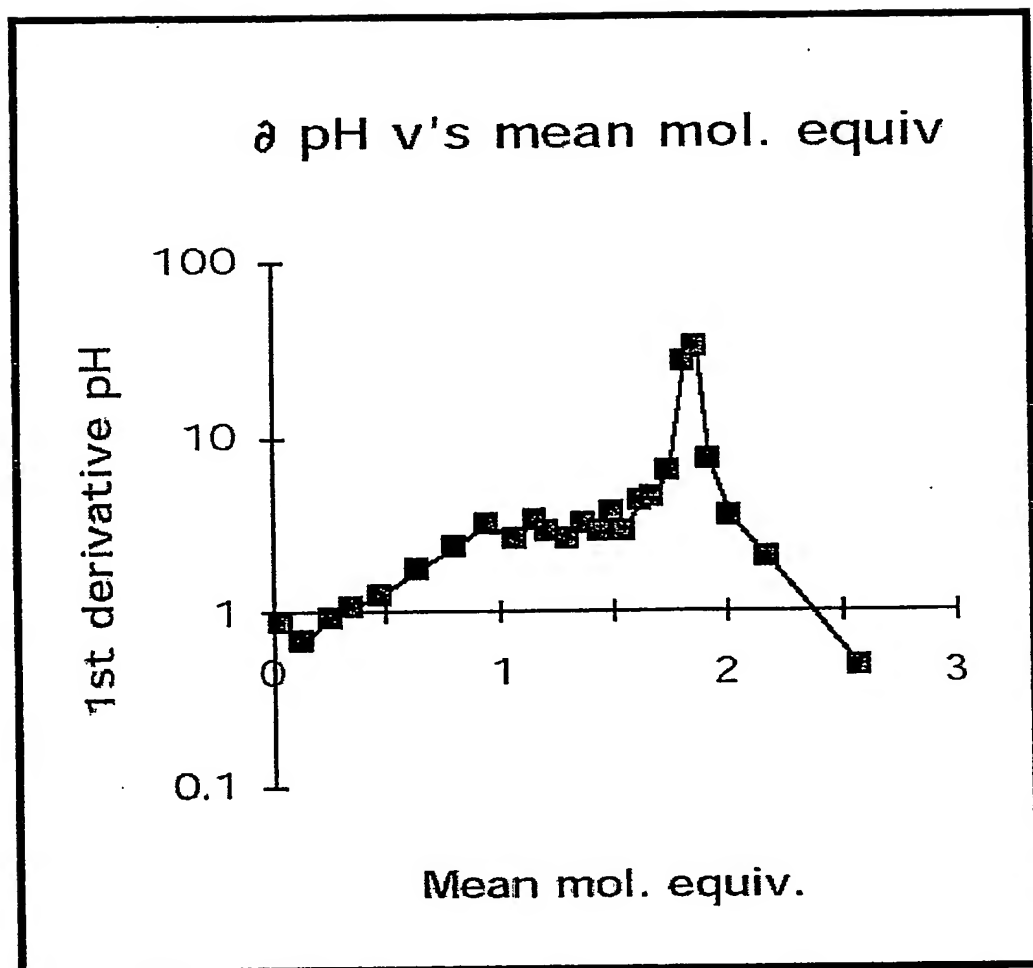


Figure 3